

Arsenic Carcinogenicity Testing

Chappell et al. (1) propose several valid ideas and procedures for accomplishing better drinking water standards for arsenic, a metalloid long known to be carcinogenic to humans (2-4). Another necessary recommendation, and in our opinion an obvious need, apparently not stated specifically in the Chappell et al. review on arsenic (1) is that we should test arsenic for long-term toxicity and carcinogenicity in laboratory animals. In our view, adequate long-term carcinogenesis bioassays have not been done on this metal or its common environmental and commercial inorganic derivatives. However, some evidence of carcinogenicity in animals has been reported but has not been associated specifically with arsenic, mainly because these experimental studies have been considered inadequate due to other confounding agents; for example, inappropriate or absent controls, and in one study arsenic was given with copper sulfate (Bordeaux mixture) to mimic the actual antifungal agent used in vineyards (4,5).

Arsenite undergoes methylation in liver nonenzymatically to methanearsonic acid and enzymatically to monomethylarsonic acid (MMA), and subsequently to dimethylarsinic acid (DMA) via oxidative addition of a methyl group with *S*-adenosylmethionine as the methyl donor. Enzymatic methylation is thought to detoxify arsenic. One reason given for the apparent lack of carcinogenicity of arsenic in animals is the methylation differential between humans and rodents. Humans excrete more MMA and less DMA, indicating effective methylation, than most rodent species (mice, rabbits, and hamsters), except rats, which display a unique biokinetics because they sequester arsenic in hemoglobin in red blood cells. This implied lower capacity to detoxify arsenic via methylation may be related to nutrition, particularly with nutrients associated with production of methyl donor groups. Nutrition appears to play an influential role in sensitivity to arsenic carcinogenesis. Poor nutrition may be the underlying reason why carcinogenic activity of arsenic is often seen in lower socioeconomic individuals. In arsenic carcinogenesis studies, we recommend the use of a diet with marginally low methyl content rather than the high protein laboratory chows currently used or available on the market. Prior carcinogenicity studies using rodents have consistently ignored this important aspect of arsenic metabolism.

Also in our view, we would suggest long-term inhalation studies using arsenic

trioxide, the most common arsenic compound considered carcinogenic to humans. This could be done in both sexes of mice (using a strain known to methylate arsenic), and perhaps in rats as well. Further, another study could be done using drinking water as the medium for administering arsenic; as suggested by Chappell et al. (1), exposure levels could be geared toward actual and multiples of drinking water levels in the environment. Of course the highest exposure levels must be those typically chosen for long-term carcinogenicity studies (6,7). In addition, these studies should be conducted for longer periods of time than the standard 104 weeks to allow the opportunity for any late-stage carcinogenic effects to be manifested; perhaps 30 months or longer would be more adequate. Additionally, some experimental efforts could be directed to initiator-promoter systems.

In another testing scenario that is more environmentally based, the same animals could be exposed to arsenic via various media simultaneously to more closely model actual conditions for humans exposed to arsenic; that is, expose groups of animals with arsenic in drinking water, in food, and by inhalation—just like humans are exposed. One should additionally use groups exposed simultaneously to chlorinated drinking water (a suspected human carcinogen for the urinary bladder), rather than the typically deionized or distilled water used in long-term drinking water experiments. These proposed long-term studies could serve at least two purposes: 1) to generate more appropriate data to allow better environmental risk assessments to be made, especially for drinking water standards (1); and 2) to best answer the long-held view that arsenic may be a paradoxical carcinogen; that is, carcinogenic to humans but not to laboratory animals. In our opinion, given that arsenic has not been studied adequately and that some earlier experiments have shown limited evidence of carcinogenic activity, the use of current experimental design conditions will show arsenic to be carcinogenic to animals.

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Environmental Lead Is a Problem in Lima, Peru

Blood lead levels as low as 10 µg/dl pose a threat to children's development (1). In Latin America's major cities, still afflicted by the massive use of leaded gasoline, prevalences above that level range from 25 to 100%.

Hitherto, no information exists on the magnitude of high blood levels in Peru. In the capital city of Lima, now with 8 million inhabitants, the most contaminated districts are those located in the northeastern sector, where most of the city's lead emissions are mobilized by a typical wind pattern. In 1991, the amount of lead particles that settled on the ground in the district of San Juan de Lurigancho was 0.015 metric tons per square kilometer in 30 days, three times higher than the upper tolerable limit (2). In 1993, the Peruvian Ministry of Health (3) reported that Lima's monthly average concentration of lead in the air (in micrograms per cubic meter) was 2.6 in April; 2.05 in May; 2.18 in June; and 1.5 on average from July through December. All exceeded the annual maximum limit of 0.5 µg/m³.

For preschool children, the lead health hazard is compounded by iron deficiency anemia, which is highly prevalent in this age group. In fact, several studies indicate that low iron stores may result in greater susceptibility to lead absorption by humans (4).